Maternal health project, South Sudan. Copyright: Matthias Steinbach

Safety of hepatitis E vaccine in pregnancy: emulating a target trial following a mass reactive vaccination campaign in South Sudan

Robin C. Nesbitt, Andrew S. Azman, Vincent Kinya Asilaza, Jessie K. Edwards , Patrick Nkemenang, Primitive Gakima, Priscillah Gitahi, Duol Biem, Fredrick Beden Loro, Jetske Duncker, Joseph F Wamala, Manuel Albela, John Rumunu, Nelly Staderini, Monica Rull, Melat Haile, Iza Ciglenecki, ***Etienne Gignoux**

Conflict of Interest:
The author has declared no conflict of interest.

Hepatitis E

- Hepatitis E exists worldwide, large outbreaks in Africa and Asia
- Self-limiting but can lead to acute liver failure and death with CFR <1% 1
- Pregnant women in the second or third trimester are at risk of acute liver failure, fetal loss and mortality with CFR up to 25%2
- No specific treatment

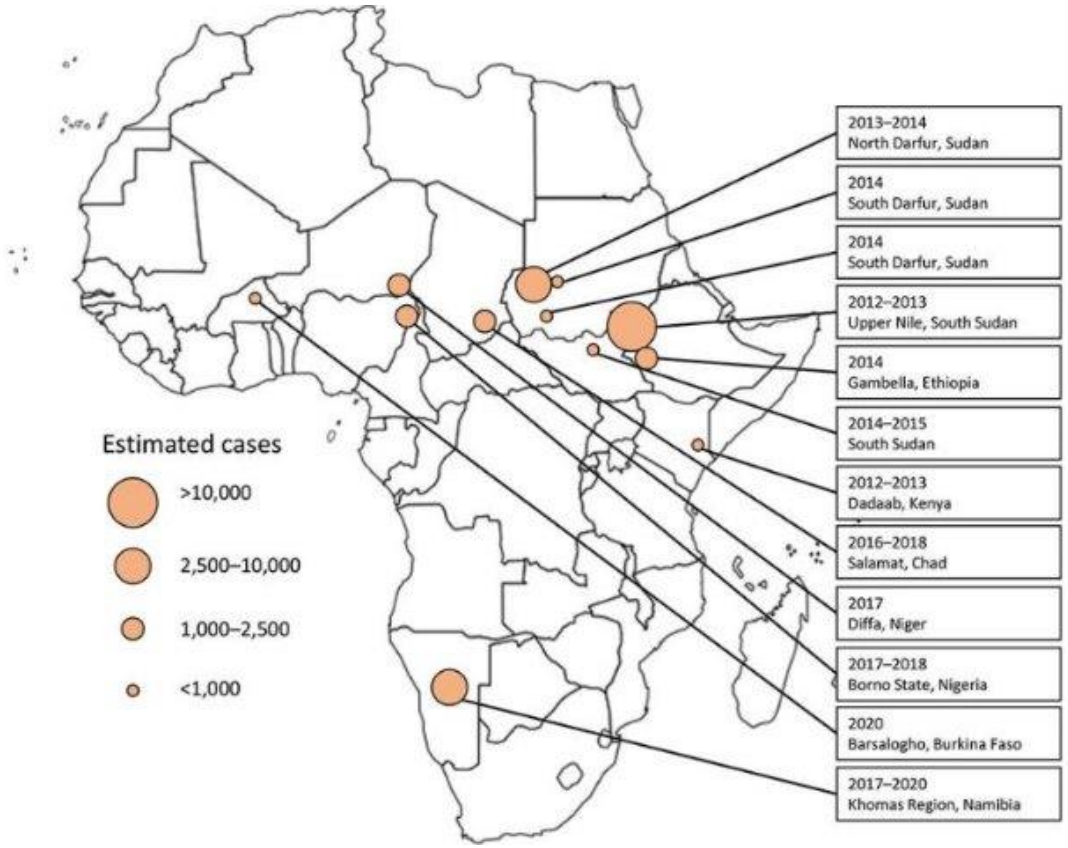
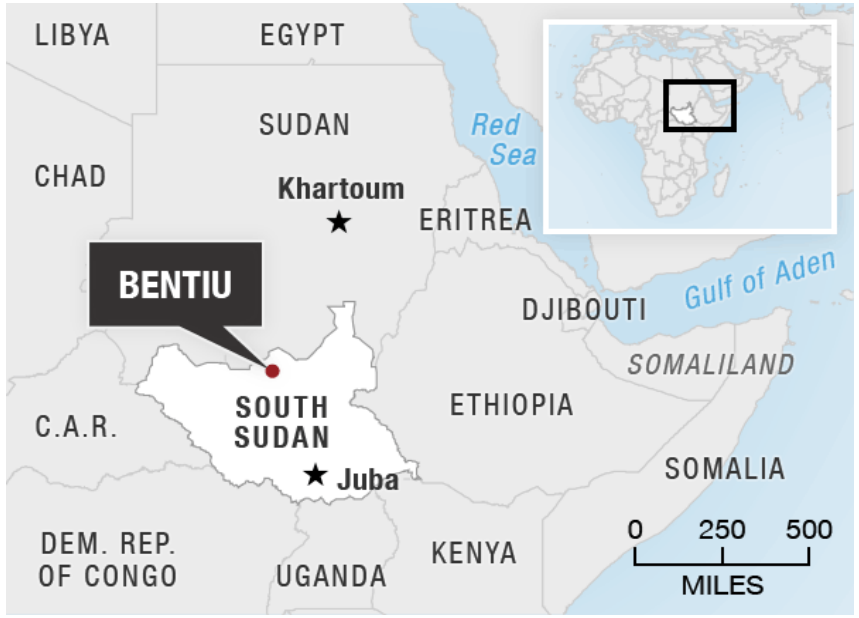


Figure 1. Geographic distribution of acute hepatitis E virus outbreaks reported among displaced persons in sub-Saharan Africa, 2010–2020
Source CDC Research Letter Viral Hepatitis E Outbreaks in Refugees and Internally Displaced Populations, sub-Saharan Africa, 2010–2020, May 2022

First mass reactive vaccination campaign against Hepatitis E

- Bentiu IDP camp, South Sudan (total population ~120,000)
- Hecolin vaccine (Innovax) 0, 1, 6 months
- Target population 16 - 40 years old residing in Bentiu IDP camp
- Including pregnant women
- 27,000 people per round
- 3 rounds: March, April, October 2022
- High administrative coverage
  - Over 90% target population vaccinated per round
  - >80,000 vaccines distributed
- Operational research
  - Feasibility
  - Vaccine effectiveness
  - **Safety in pregnancy**

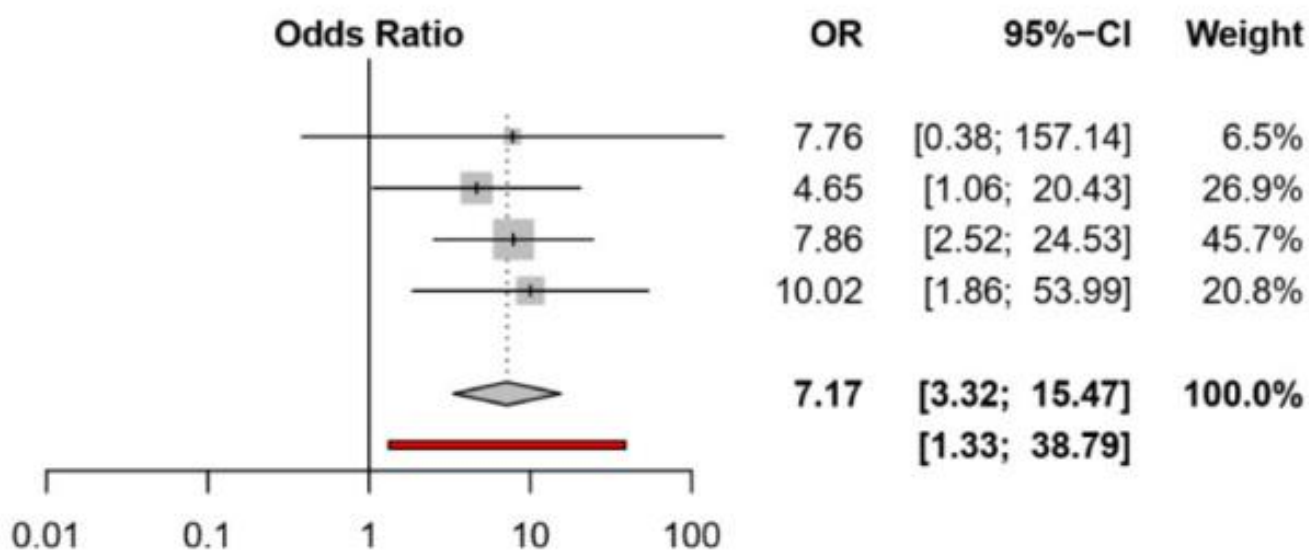

Aerial view of Bentiu. Copyright: Njiiri Karago/MSF



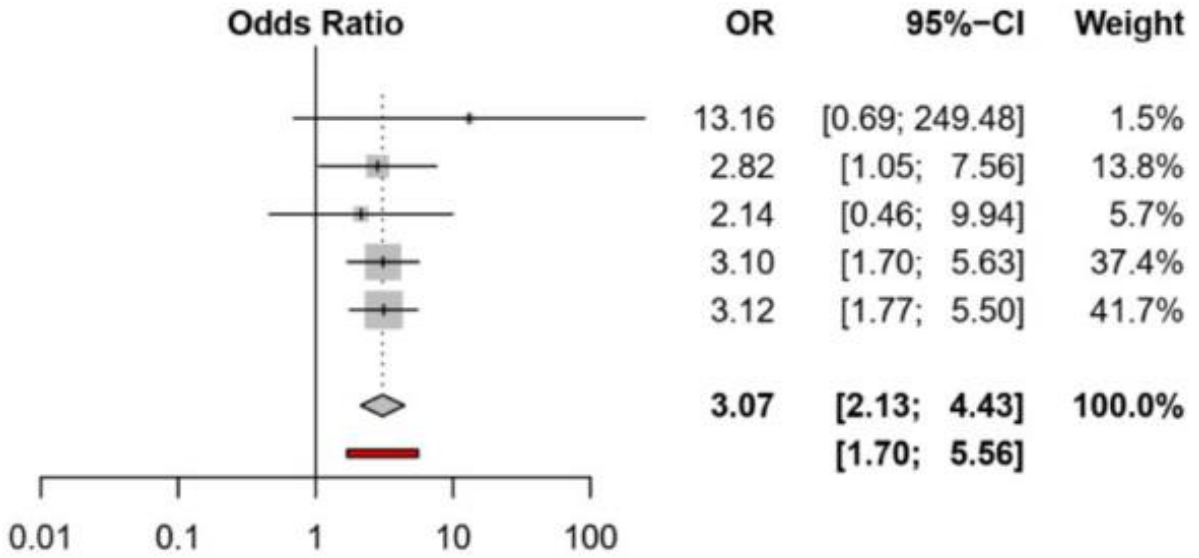
Hepatitis E in pregnancy

Hepatitis E increases risk of maternal death and adverse pregnancy outcomes[1]

Maternal death: Odds Ratio 7.17



Intrauterine death: Odds Ratio 3.07



[1]Bigna et al. BMC Pregnancy and Childbirth 2020

Hepatitis E vaccine in pregnancy

Evidence gap on safety of Hecolin® vaccine in pregnancy

Hepatitis E vaccine. Copyright: MSF

Method	Primary exposure	Comparison arm	Number of pregnant women inadvertently exposed	Results	Reference
Phase 3 trial	Hecolin	Hep B	37 pregnant women	No SAEFI	Wu, Hepatology, 2012
Phase 3 trial	HPV	Hecolin	66 pregnant women	No SAEFI	Zhao, Lancet CID, 2022
Phase 4 trial	Hecolin	Hep B	Pending	Pending	Zaman, BMJ Open, 2020

Aim: Evaluate vaccine safety in pregnancy

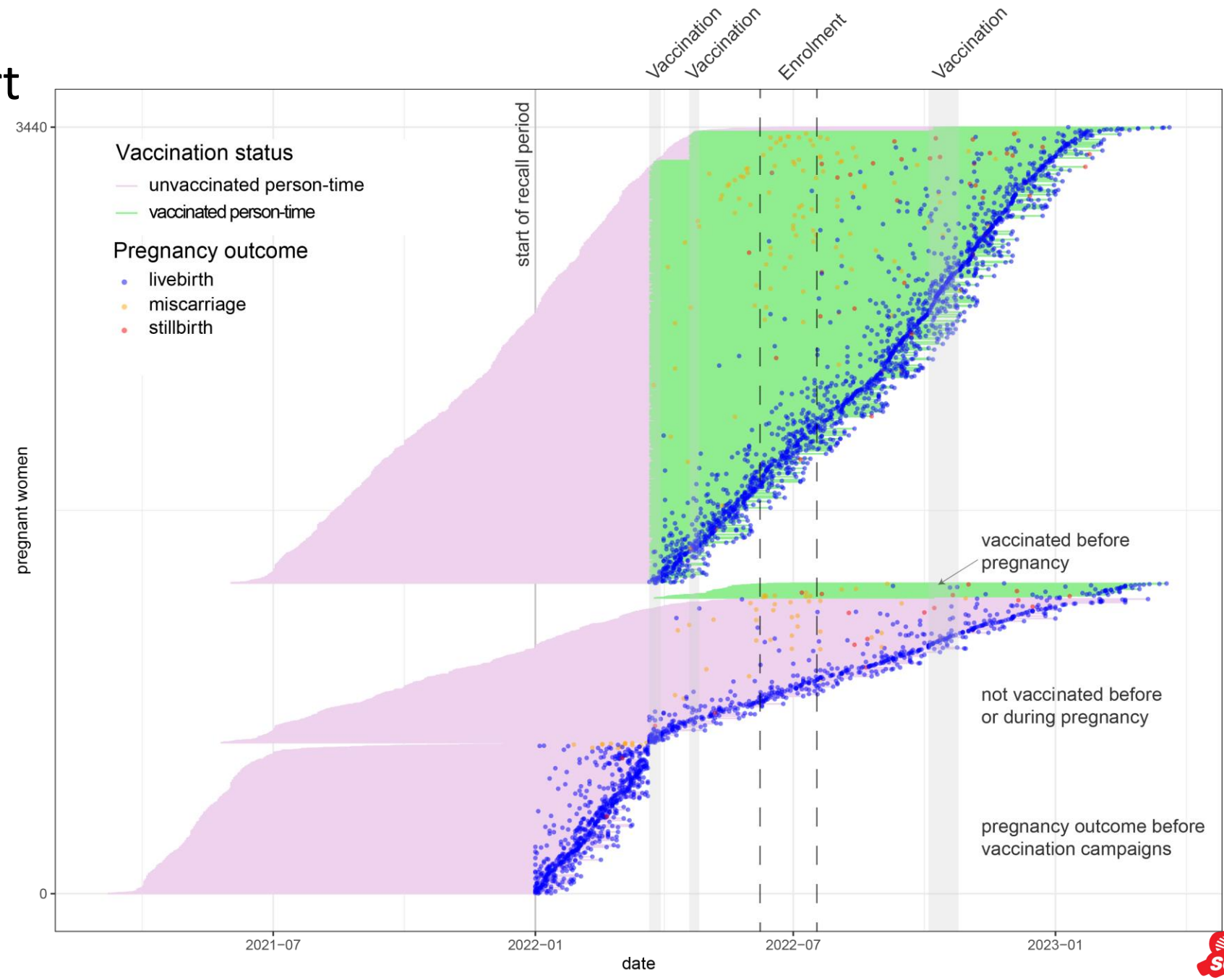
Research questions:

1. Does vaccination against hepatitis E *during pregnancy* increase the risk of fetal loss?
2. Does vaccination against hepatitis E *prior to conception* increase the risk of fetal loss?

Methods: Pregnancy census and cohort

- Census of entire Bentiu IDP camp after second vaccination round (May-June 2022)
- Women with **known self-reported pregnancy** between 1 January and interview
- Home visit 28 days after delivery for pregnancy outcome information

Pregnancy cohort



Crude results: Exposure during pregnancy

- 76% vaccination during pregnancy
- 6.9% fetal loss (miscarriage or stillbirth)
- Differences by vaccination status
  - ANC attendance
  - Jaundice during pregnancy
- No difference in fetal outcome
  - Combined negative fetal outcome (miscarriage + stillbirth) p= 0.54

	Not vaccinated pregnancy (n=638)	Vaccinated during pregnancy (n=2036)	P-value
Mean age enrolment (SD)	25.1 (6.09)	25.4 (6.20)	0.23
Attended ANC	507 (79.5%)	1783 (87.6%)	0.0005
Jaundice during pregnancy	8 (1.3%)	6 (0.3%)	0.019
Malaria during pregnancy	245 (38.4%)	753 (37.0%)	0.54
Complication during delivery	53 (8.3%)	209 (10.3%)	0.12
Cesarean section	4 (0.6%)	9 (0.4%)	0.65
Gravidity			
Mean (SD)	2.35 (2.17)	2.57 (2.15)	0.029
Median [Min, Max]	2.00 [0, 9.00]	2.00 [0, 11.0]	
Fetal outcome			
Livebirth	598 (93.7%)	1892 (92.9%)	0.80
Miscarriage	29 (4.5%)	107 (5.3%)	
Stillbirth	11 (1.7%)	37 (1.8%)	

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Crude results: Exposure prior to conception

- Higher proportion of fetal loss overall (77.5% livebirth)
- None of the women vaccinated prior to conception reported jaundice during pregnancy
- No difference in fetal outcome between two groups
  - Combined negative fetal outcome (miscarriage + stillbirth) p=0.82

	Vaccinated before conception N=67	Not vaccinated before conception N=44	P-value
Mean age enrolment (SD)	26.2 (6.8)	25.1 (6.2)	0.35
Attended ANC	30 (44.8%)	22 (50.0%)	0.70
Malaria during pregnancy	16 (23.9%)	14 (31.8%)	0.39
Complication during delivery	8 (11.9%)	3 (6.8%)	0.52
Gravidity			
Mean (SD)	2.6 (2.2)	2.55 (2.3)	0.91
Median [Min, Max]	2.0 [0, 8.0]	2.0 [0, 9.0]	
Fetal outcome			
Livebirth	51 (76.1%)	35 (79.5%)	0.95
Miscarriage	10 (14.9%)	6 (13.6%)	
Stillbirth	6 (9.0%)	3 (6.8%)	

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Analysis methods

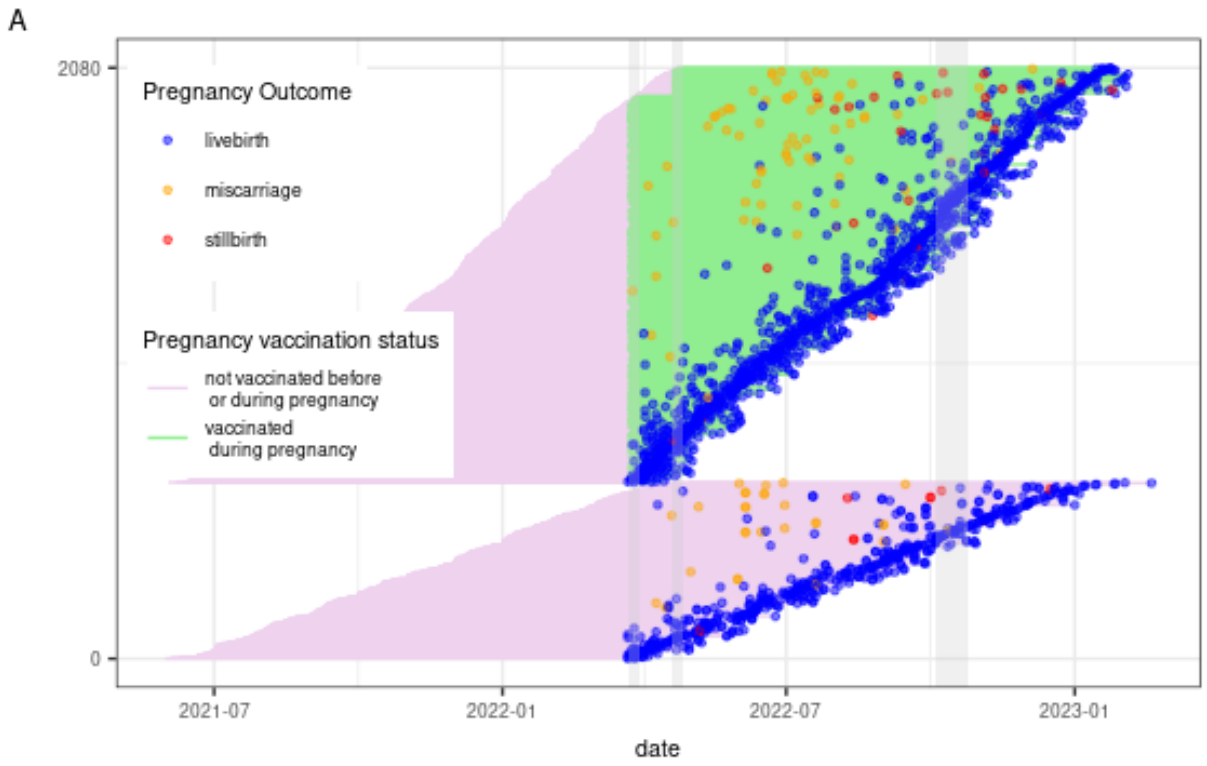
- Emulated target trial framework
- Matching vaccinated to unvaccinated pregnant women (with replacement)
  - Step one: Each vaccinated woman is matched to unvaccinated women on the following criteria:
    - Age at inclusion (+/- 1 year)
    - Gestational age at vaccination (+/- 1 week)
    - Must be pregnant at time of vaccination
  - Step two: From all possible matches, woman with the closest propensity score to be vaccinated is selected
- Women who were vaccinated during the second round in April were considered unvaccinated and eligible to be matched as unvaccinated until their vaccination date, when they both members of the vaccinated pair were censored
- Inverse probability of censoring weights to account for this informative censoring
- Aalen-Johansen estimator to estimate the cumulative incidence functions using time of vaccination for index women as the time origin for each matched pair

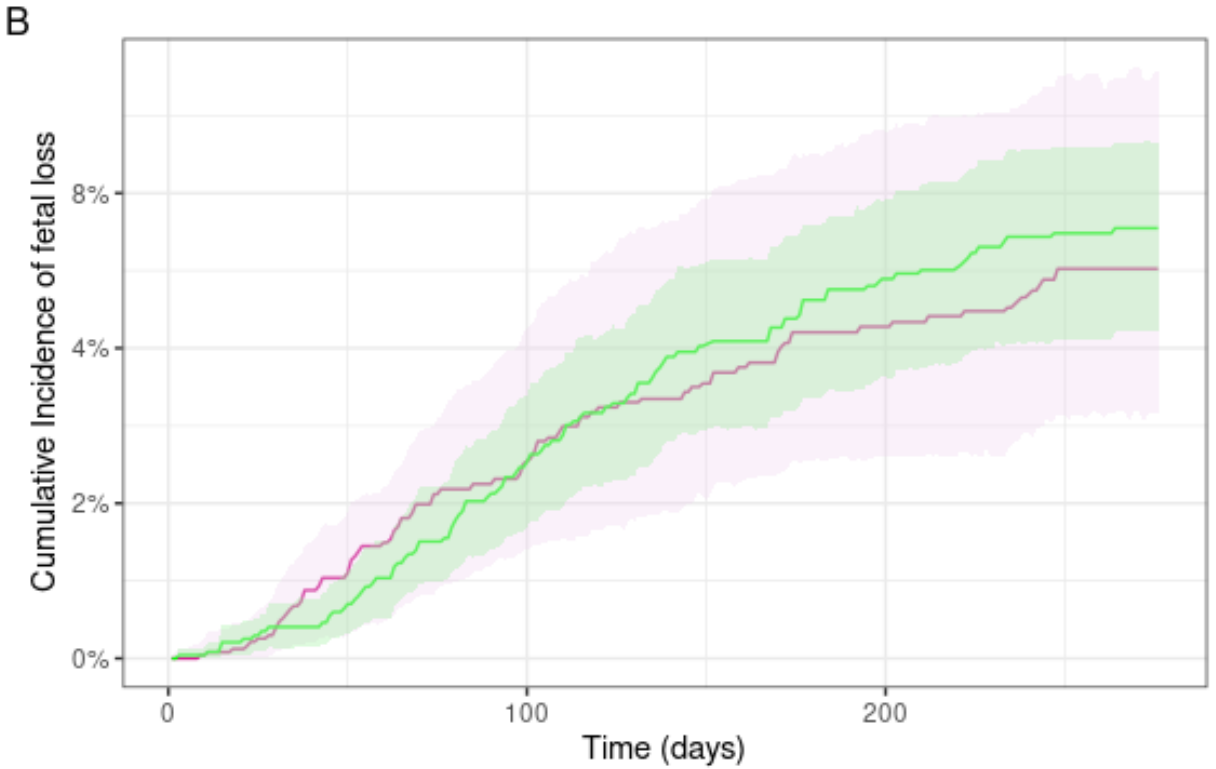
Results: Matched analysis

- No evidence of increased risk of fetal loss among vaccinated women
- Sensitivity analyses with different matching criteria show no qualitative differences

	Vaccinated		Unvaccinated			
Exposure period	**Matched/Total**	**Risk (95%CI)**	**Matched/Total**	**Risk (95%CI)**	**RR**	**95% CI**
Pregnancy	1928/2036	6.9 (5.3, 8.32)	479/638	6.3 (4.0, 9.4)	1.1	(0.66, 1.8)
Pre-conception	45/67	20.0 (6.3, 34.5)	21/44	20.0 (5.4, 52.5)	1.0	(0.22, 3.3)
Bias indicator: post-partum	460/553	0.43 (0, 1.2)	100/127	0 (0, 0)	–	–

Results : Matched analysis exposure during pregnancy





MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Discussion


Nyalam delivered Pim in Nasir PHCC, South Sudan
Copyright: Brendan Bannon/MSF

No evidence of increased risk of fetal loss due to vaccination

- During pregnancy or before conception

Access to delivery care is high in Bentiu IDP camp

- Facility delivery 90% in Bentiu IDP camp vs. 19% for South Sudan

Maternal and fetal outcomes better than national average

- Stillbirth rate 17 per 1,000 pregnancies in Bentiu vs. 30 per 1000 pregnancies in South Sudan
- Maternal mortality ratio ~ 135 per 100,000 in Bentiu vs. 789 -1223 deaths per 100,000 in South Sudan

Discussion

Strengths

- Outcomes for >2000 women vaccinated during pregnancy in real world setting
- Causal approach used to estimate effect size (emulated target trial)
- Consistent qualitative results throughout analyses using different approaches/assumptions

Limitations

- Observational study
- Imperfect determination of start of pregnancy
- Vaccination status through self-report (often verified with vaccination cards)
- Additional pregnancy outcomes (preterm birth, LBW) not available

Conclusions

- No evidence of increased risk of fetal loss due to vaccination during or before pregnancy in context of high use of ANC and facility delivery
- Results contributed to 2024 WHO SAGE recommendations on use of HEV vaccine among pregnant women
- Second reactive vaccination campaign underway in Old Fangak, South Sudan

A woman carrying her child in a basket, South Sudan. Copyright: Brendan Bannon/MSF

Sundown at the MSF Hospital in Bentiu. Copyright: Peter Bauza/MSF

Acknowledgements

Thank you to the South Sudan Ministry of Health, World Health Organization, health partners in Bentiu, MSF OCA and OCG in Bentiu, Juba, Amsterdam and Geneva

Thank you to the Bentiu IDP camp Community High Commission and the entire population of Bentiu IDP camp

Thank you to MSF OCG Bentiu Hepatitis E vaccination team

Thank you to MSF OCG Bentiu study team

Vincent Kinya, Epidemiology Activity Manager

Doki Simon, Epidemology Activity Manager

Chuol Phar Met, Data processing Officer

Stephen Yoal Makon Machar, Clinical Research Assistant

Nyadiet Priscilla Luony, Clinical Research Assistant

Malual Nguen Chuol, Lab technician

Gatmai Reer,Survey team supervisor

Entire survey team